October 4, 2002

Elizabeth K. Hunt
Executive Director
Thioesters Assocation
941 Rhonda Place S.E.
Leesburg, VA 20175

Dear Ms. Hunt:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Thiodipropionates Category posted on the ChemRTK HPV Challenge Program Web site on January 15, 2002. I commend the Thioesters Association for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Thioesters Association advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Thiodipropionates Category

SUMMARY OF EPA COMMENTS

The sponsor, the Thioesters Association, submitted a test plan and robust summaries to EPA for the thiodipropionates category dated December 14, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on 15 January 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category is acceptable.

2. Physicochemical Properties and Environmental Fate. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

3. Health Endpoints. All appropriate SIDS-level tests have been performed. EPA agrees that no additional health effects testing is necessary. The submitter needs to address some deficiencies in the robust summaries.

4. Ecotoxicity. EPA agrees that no further ecotoxicity testing is necessary due to the extremely low water solubility and high estimated log K_{ow} values of the category members.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THIODIPROPIONATES CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposes a category covering three thiodipropionates that are symmetrically esterified by two linear aliphatic groups ranging in size from C_{12} to C_{18}. These compounds are: 3,3'-thiodipropionic acid didodecyl ester (CAS No. 123-28-4), 3,3'-thiodipropionic acid dioctadecyl ester (CAS No. 693-36-7), and 3,3'-thiodipropionic acid ditridecyl ester (CAS No. 10595-72-9).

Category Justification

The submitter's primary justification for the category is based on the expectation that the close structural similarity should result in properties that are either similar or follow a pattern that correlates with changes in the molecular weights of the compounds. The category members are high-molecular weight dithiopropionate esters that differ only in the chain length (C_{12}-C_{18}) of the dialkyl ester functions and are expected to follow a regular pattern for all SIDS-level endpoints. Based on the structures and molecular weights of the category members, as well as available data on category members, EPA agrees that

predictive methods and extrapolation and interpolation of data within the category are acceptable. Data provided by the submitter also demonstrate that these compounds generally have mammalian toxicities that are similar (*e.g.*, acute oral LD_{50}, acute irritation thresholds, and genotoxicities) or follow a pattern that parallels changes in molecular weight (*e.g.*, repeated-dose NOAEL).

Justification of the category partly on the basis of similar toxicological properties is supported in the test plan by similar results in acute data available on all three compounds. In addition, genotoxicity assays were negative for the two group members that were tested. The submitter also provided results of acute eye and skin irritation and sensitization studies for the latter two substances, as well as repeated-dose studies. These data indicate similar results for the two compounds. Similar toxicological results are expected for the category members, based on the similarities in structure, size and solubility (especially $\log K_{OW} > 10$), which are properties that directly affect absorption and distribution. EPA agrees that the category is adequately supported based on chemical structure and available data.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available on the didodecyl ester for all health effects endpoints, on the dioctadecyl ester for acute, repeated-dose and genetic toxicity, and on the ditridecyl ester for acute toxicity only. EPA agrees with the submitter's plan to address data gaps by extrapolation from existing data and that no additional health effects testing is needed.

Acute Toxicity. EPA agrees that no additional acute toxicity testing is needed based on the weight of the evidence for data submitted for all three category members.

Repeated-Dose Toxicity. EPA agrees that no additional repeated-dose toxicity testing is necessary based on the adequate data submitted for 3,3'-thiodipropionic acid didodecyl ester and 3,3'-thiodipropionic acid dioctadecyl ester.

In the test plan (Matrix table, page 2/23 and Table 6, page 16/23), the submitter estimated a NOAEL of ~1125 mg/kg/day for 0.400 kg Fisher rats exposed to 3% 3,3'-thiodipropionic acid dioctadecyl ester in feed for two years. The submitter needs to provide the details of this calculation.

Genetic Toxicity. EPA agrees that no additional genotoxicity testing is needed based on the adequate data submitted for 3,3'-thiodipropionic acid didodecyl ester and 3,3'-thiodipropionic acid dioctadecyl ester.

Reproductive Toxicity. EPA agrees that no further reproductive toxicity testing is needed for the category based on adequate data submitted for 3,3'-thiodipropionic acid didodecyl ester.

Developmental Toxicity. EPA agrees that no additional developmental toxicity testing is needed based on the data for four animal species submitted for 3,3'-thiodipropionic acid didodecyl ester.

Ecotoxicity

Although the submitted test data are inadequate, EPA agrees with the submitter's test plan to conduct no further testing of category members for acute effects because of their extremely low water solubility. In

addition, the high estimated log K_{ow} values for the chemicals preclude the need for chronic ecotoxicity testing.

Specific Comments on the Robust Summaries

General Comment

The IUCLID data set for 3,3'-thiodipropionic acid dioctadecyl ester did not list the purity of the compound.

The IUCLID data set for 3,3'-thiodipropionic acid ditridecyl ester lists the wrong CAS. No. in the id header on pages 14/37-22/37

Health Effects

Acute Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The three olive oil vehicle studies did not report the length of the observation period or indicate whether the animals were evaluated for systemic effects aside from mortality.

3,3'-Thiodipropionic acid dioctadecyl ester. The submitter submitted data for four acute toxicity studies (3 in rats and 1 in mice). Information omitted included the gavage vehicle, the length of the observation period, and results for systemic toxicity.

Repeated-Dose Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The robust summary did not report the gavage vehicle or the specific differences in outcomes following exposure at the NOAEL (350 mg/kg/day) and the NOEL (125 mg/kg/day).

3,3'-Thiodipropionic acid dioctadecyl ester. The robust summary for the 2-year feeding study omitted the animals' sex and incidence data for the observed body weight effects. Also, the summary did not include the submitter's estimation of daily dose (mg/kg/day) that was reported in the test plan (tables on pages 2/23 and 16/23).

Genetic Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The robust summary for mutation in bacterial cells did not report the positive control or the source of the S9 used for metabolic activation.

The robust summary for the *in vivo* micronucleus assay in rats did not report whether there was any effect on the mitotic index.

3,3'-Thiodipropionic acid dioctadecyl ester. The robust summaries for both studies did not report the source of the metabolic activation system and the purity of the test material.

Reproductive Toxicity. 3,3'-Thiodipropionic acid didodecyl ester. The robust summary did not state the

gavage vehicle.

Developmental Toxicity. 3,3'-Thiodipropionic acid didodecyl ester. Robust summaries for all four studies were complete except for the gavage vehicle and the purity of the test substance.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.